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A Convenient Means of Generating Alkyl-Substituted Isobenzofurans as Reactive Intermediates

J. G. Smith* and R. T. Wikman

Department of Chemistry, University of Waterloo, Waterloo, Ontario, Canada

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A tautomeric equilibrium is demonstrated to exist between 1-benzalphthalan and 1-benzylisobenzofuran. This equilibrium is exploited as a convenient means of generating alkyl-substituted isobenzofurans as reactive intermediates and the same principle is employed to prepare 1-*tert*-butyl-3-phenylisobenzofuran. Examples are given of the use of these isobenzofuran derivates to prepare substituted naphthalenes and a naphthol. The generation of substituted isobenzofurans by the procedure described here has the advantage that the initial reagents are readily prepared and the generation of the isobenzofuran is not accompanied by any coproduct.

The facile oxidation[1,2] of benzalphthalan, **1a**, is inconsistent with its structure. However, this reactivity suggested that an equilibrium might exist between **1a** and its tautomer 2-benzylisobenzofuran, **2a**. Subsequent reactions then proceed through this reactive[3] intermediate.

The existence of this equilibrium was established by capturing the intermediate **2a** through a Diels–Alder reaction with dimethyl acetylenedicarboxylate to provide **3a**. Attempts to observe directly this equilibrium by nmr or uv spectroscopy were unsuccessful.

In pursuit of a directly observable equilibrium, compounds containing one phenyl substituent were prepared. Thus dehydration of the hydroxyphthalan **5b** gave **1b** which in the presence of dimethyl acetylenedicarboxylate formed the Diels–Alder adduct **3b**. Unfortunately, the isobenzofuran **2b** could not be detected spectroscopically.

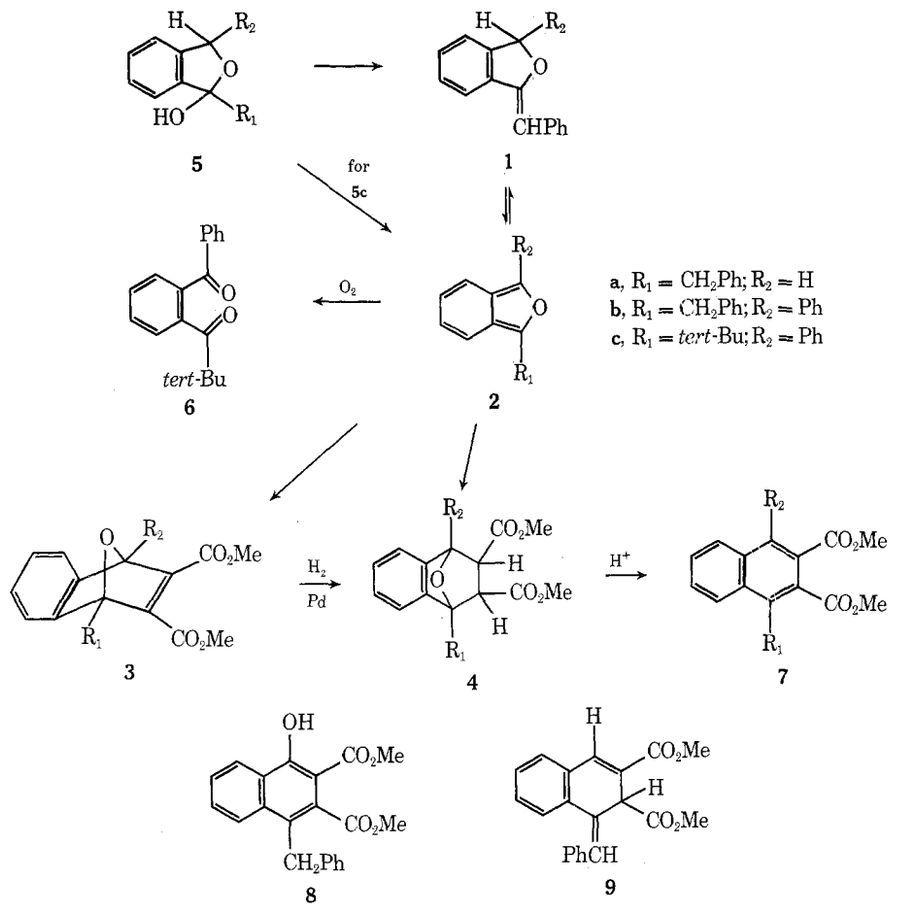
In the case of the hydroxyphthalan **5c**, dehydration of necessity produced the corresponding isobenzofuran **2c**, isolated as a reactive yellow oil with a brilliant fluorescence under uv light. The isobenzofuran structure was supported by its uv spectrum, by its easy oxidation[4] to the diketone **6**, and by the reaction of **2c** with dimethyl acetylenedicarboxylate and dimethyl maleate to produce **3c** and **4c**, respectively (maleic anhydride also reacts).

The accessibility of isobenzofurans as reactive intermediates has important synthetic consequences. Thus substituted naphthols can be formed by acid-catalyzed ring opening[5] of **3** and the reaction **3a** to **8** was effected here. Again, substituted naphthalenes[5,6] can be obtained by ring opening of compounds such as **4**, which, in turn, are prepared from **2** and dimethyl maleate (*e.g.*, **4c**) or by hydrogenation of **3** (*e.g.*, **3a** and **3b**). The ring openings are sensitive to the substituent groups present. While **4b** was transformed smoothly to **7b**, **4c** resisted conversion to the corresponding naphthalene perhaps because of the steric crowding which would arise in the product from the coplanarity of the substituent groups, the peri interactions being exaggerated by the buttressing effects of the carbomethoxy groups. On the other hand, **4a** was converted to a mixture containing **7a** as the major product and **9** as the minor product. Since **7a** and **9** are not in equilibrium, these products must arise by competitive eliminations. This suggests that the stereochemistry of **4** or the conformation of the intermediates are an important factor in this reaction.

In this regard, **4a** has the endo configuration since coupling is observed between the bridgehead hydrogen and the hydrogen α to the carbomethoxy group. It is suggested that **4b** and **4c** have the more stable exo configuration since attempts to isomerize these compounds have been unsuccessful.

The utilization of isobenzofuran[3,6b,7] as a reactive intermediate in syntheses has been reported elsewhere. These methods generally involve the initial preparation of Diels–Alder adducts which decompose photolytically or thermally to provide the desired intermediate. The approach described here has the advantage that the initial reagents are readily prepared and no coproduct is generated on forming the isobenzofuran.

Scheme I
Formation and Detection of the Isobenzofuran Derivatives



5 1 6 2 3 4 7 8 9

Experimental Section

Melting points are uncorrected. Spectra were recorded on Beckmann IR 10, Unicam SP-800, and Varian T-60 spectrometers. Nmr spectra were determined in $CDCl_3$ and are reported in ppm downfield from TMS as internal standard (δ scale). Infrared spectra were measured in KBr unless otherwise specified. Analyses were performed by MHW Laboratories, Garden City, Mich.

Benzalphthalan (1, R_2 = H) and 1-benzyl-1-hydroxyphthalan (**5a**) were prepared as described elsewhere.[2] The hydroxyphthalans **5b** and **5c** were not isolated because of their facile dehydration but were converted directly to the products **1** (R_2 = Ph) and **2c**, respectively.

Preparation of 1-Benzal-3-phenylphthalan 1 (R_2 = Ph). The Grignard reagent, prepared from 2.78 g (0.022 mol) of benzyl chloride and 0.61 g (0.025 g-atom) of magnesium in 50 ml of DEE, was added to 4.20 g (0.02 mol) of 3-phenylphthalide[8] in 50 ml of DEE. After 8 hr at 20° the mixture was hydrolyzed with aqueous NH_4Cl and the ether layer separated, dried, and evaporated. Normally, the diastereomeric alcohols[5b] were not purified but immediately dehydrated. In one instance, the material was purified by precipitation from benzene solution with hexane: nmr 3.40 and 3.47 (s, 2, $PhCH_2$), 5.72 and 6.25 (s, 1, PhCH), 7.0–7.6 (m, 14, aromatics).

Dehydration was effected by warming **5b** *in benzene containing* a catalytic quantity of *p*-toluenesulfonic acid (TsOH). Evaporation gave a quantitative yield of 1 (R_2 = Ph) which was sufficiently pure for subsequent use. The analytical sample was obtained by four recrystallizations from ether–pentane: mp 119° dec; nmr 6.04 (s, 1, *tert*-H), 6.58 (s, 1, vinyl H), 7–8 (m, 14, aromatic H); ir (KBr) 1650 (C=C), 1500, 810, 750, 690 (aromatic).

Anal. Calcd for $C_{21}H_{16}O$: C, 88.70; H, 5.67. Found: C, 88.93; H, 5.63.

Preparation of 1-*tert*-Butyl-3-phenylisobenzofuran, 2c. The Grignard reagent, prepared from 2.8 g (0.03 mol) of *tert*-butyl chloride and 0.85 g (0.035 g-atom) of magnesium in 50 ml of DEE, was added to 4.20 g (0.02 mol) of 3-phenylphthalide[8] in 50 ml of DEE at 20°. After 12 hr, the mixture was hydrolyzed with aqueous NH_4Cl and the ether layer separated, dried, and concentrated.

The nmr spectrum of the product at this stage showed resonance peaks characteristic of the starting phthalide, the isobenzofuran **2c**, and a *tert*-butyl peak at 1.55 assigned to **5c**. The reaction product was dissolved in 100 ml of benzene, treated with 5 mg of TsOH, concentrated, and applied to a chromatographic column of 100 g of silica gel and elution carried out with benzene. The isobenzofuran eluted first and was readily located by its intense fluorescence under uv light (366 nm). Concentration of the eluate gave 2.2–2.6 g (44–52%) of **2c** as an oil: nmr 1.52 (s, 9, *tert*-**Bu**), 6.6–7.9 (m, 9, aromatic **H**);[9] ir (film) 2960 (aliphatic CH), 1600, 1500, 760, 740, 680, 660 (aromatic) cm^{-1}; uv (MeOH) λ (ϵ), 265 (6.5×10^3), 275 (6.4×10^3), 286 (5.8×10^3), 305 (3.8×10^3), 319 (4.9×10^3), 336 (5.3×10^3), 364 (10^4) nm.

Anal. Calcd for $C_{18}H_{18}O$: C, 86.35; H, 7.26. Found: C, 86.26; H, 7.16.

Diels–Alder Reactions. The Diels–Alder reactions were conducted in refluxing DEE containing a catalytic amount of acid with the isobenzofuran precursors (**1**, R_2 = H or Ph) or **2c** and an equivalent amount or excess of the dienophile. Washing the solution with aqueous $NaHCO_3$, evaporation, and recrystallization provided the products shown in Table I. In some cases, the product **4** in Table I were made by hydrogenation of **3**. Hydrogenation was effected in ethyl acetate using 5% Pd on charcoal as catalyst at 50 psi hydrogen pressure.

No change occurred in compounds **4b** and **4c** on refluxing in xylene for 12 hr.

Naphthalene Derivatives. The products 4 were converted to their corresponding naphthalene derivatives by refluxing in the presence of acid. The results are summarized in Table II.

Oxidation of 1-*tert*-Butyl-3-phenylisobenzofuran, 2c. Treatment of 4.26 g (0.017 mol) of **2c** with sodium dichromate in aqueous sulfuric acid gave 4.08 g of product. Distillation provided 1.95 g (43%) of **6**: bp 146–150° (0.3 mm); nmr 1.27 (s, 9), 7.2–8.0 (m, 9); ir (film) 1690 and 1660 (C = 0), 1270, 1600, 760, 700 (aromatics).

Table I
Diels–Alder Adducts and Related Compounds

Compd[a]	Yd, %	Mp, °C	Nmr, [ir]
3a	70	141–142.5	3.99 (s) and 4.02 (s) (total 6) overlaps 3.85 and 4.25 (ABq, J = 17 Hz, 2), 6.02 (s, 1) 7.0–7.6 (m, 9) [1720 (broad, C=O), 1620 (C=C), 1300 (C–O), 1500, 760, 750, 700 (aromatics)]
3b	49[b]	140–141.5	3.62 (s, 3), 3.67 (s, 3), 3.78 and 4.13 (ABq, J = 16 Hz), 7.0–7.9 (m, 14) [1720 (C=O), 1250 (C–O), 1630, 1500, 740, 700 (aromatics)]
3c	80	128–129	1.32 (s, 9), 3.56 (s, 3), 3.76 (s, 3), 7.0–8.0 (m, 9) [1730 (C=O), 1250 (C–O), 1620 (C=C), 750 and 700 (aromatics)]
4a	93[d]	110–111	3.39 (s), 3.44 (s), overlapping 3.1–3.9 (m) (total 10), 4.91 (d, J = 5 Hz, 1), 7.2–7.6 (m, 9) [1750 and 1730 (C=O), 1150 and 1210 (broad, C–O), 1500, 760, 730, 700 (aromatics)]
4b	94[d]	125.5–127 (90–92)[g]	3.47 (s, 3), 3.53 (s, 3), overlapping ABq, 3.48 and 3.77 (J = 12 Hz, and broad s), 3.77 (4) 7.2–7.9 (m, 12). [1740 (C=O), 1200 (broad, C–O), 1500, 750, 690 (aromatics)]
4c	95[d] 92[c] 75[e]	151–152	1.32 (s, 9), 3.50 (s, 6), 3.98 (s, 2), 7.2–7.8 (m, 9) [1750 and 1735 (C=O), 1200 (broad, C–O), 760, 700 (aromatics)]
f	83	147.5–148	1.39 (s, 9), 4.18 (s, 2), 6.9–8.1 (m, 9)

[a] Satisfactory analytical data were reported for all new compounds listed here. [b] Based on phenylphthalide. [c] Diels–Alder reaction using dimethyl maleate. [d] Hydrogenation of corresponding **3**. [e] Reduction of **4c** by zinc in refluxing concentrated HCl. [f] Diels–Alder adduct with maleic anhydride. [g] Mp obtained from EtOH–H_2O; mixture mp not depressed.

Table II
Preparation of Naphthalene Derivatives

Compd[a]	Conditions	Yd, %	Mp, °C	Nmr [ir]
7a	C_6H_6/TsOH	70[b]	101.5–102.5	3.92 (s) and 3.95 (s) (total 6), 4.50 (s, 2), 7.23 (s, 5), 7.2–8.2 (m, 4), 8.53 (s, 1, peri H) [1720 (broad, C=O), 1440, 1280, 1200, 1130, 780, 730, 700, 680]
7b	MeOH/HCl	93	157–158	3.52 (s, 3), 3.85 (s, 3), 4.68 (s, 2), 7.2–8.4 (m, 14)
7c	Xylene/TsOH	No reaction		
9	See **7a**		139–140	3.65 (s, 3), 3.80 (s, 3), 5.21 (s, 1), 7.13 (s, 1), 7.3–7.9 (m, 5) [1730 and 1710 (C=O), 1200 (broad, C–O), 750 and 700 (aromatics)]

[a] Satisfactory analytical data were reported for all new compounds listed here. [b] Isolated; reaction mixture contains ~80% **7a** and ~20% **9** by nmr. Both **7a** and **9** are unchanged in refluxing C_6H_6/TsOH.

Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.20; H, 6.86.

Preparation of 8. The Diels–Alder adduct **3a** (1.0 g, 0.0029 mol) was refluxed in a mixture of 25 ml of methanol and 10 ml of concentrated hydrochloric acid. The reaction product was isolated by ether extraction and purified by chromatography on silica gel. The initial fraction, 0.69 g (69%), was **8**, mp 113.5–115.5°. Recrystallization from ethanol–water gave the analytical sample: mp 115–116°; nmr 3.82 (s, 3), 3.93 (s, 3), 4.30 (s, 2), 7.13 (s, 5), 7.4–8.6 (m, 4), 12.45 (s, 1); ir 3450 (broad, OH), 1740 (C = 0), 1660 (C = 0), 810, 760, 710 (aromatics).

Anal. Calcd for $C_{21}H_{18}O_5$: C, 71.99; H, 5.18. Found: C, 72.22; H, 5.22.

Registry No.—**1** (R_2 = Ph), 52540-37-1; **2c**, 52540-38-2; **3a**, 52540-39-3; **3b**, 52540-08-6; **3c**, 52540-09-7; **4a**, 52540-40-6; **4b**, 52540-10-0; **4c**, 52540-11-1; *cis*-**5b**, 52540-12-2; *trans*-**5b**, 52540-13-3; **5c**, 52540-14-4; **6**, 52540-15-5; **7a**, 52540-41-7; **7b**, 52540-16-6;

7c, 52540-17-7; 8, 52540-18-8; 9, 52540-42-8; 3-phenylphthalide, 5398-11-8.

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The Synthesis of 2-Substituted Derivatives of 5-Amino-1-β-D-ribofuranosylimidazole-4-carboxamide. Ring Opening Reactions of 2-Azapurine Nucleosides

George A. Ivanovics, Robert J. Rousseau, Masajiro Kawana, Prem C. Srivastava,* and Roland K. Robins

ICN Pharmaceuticals, Inc., Nucleic Acid Research Institute, Irvine, California 92664

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The reaction of 5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (**1a**) with *N*-bromoacetamide gave the corresponding 2-bromo nucleoside (**3**). The latter compound was ring closed with nitrous acid to afford 6-bromo-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[4,5-*d*]-*v*-triazin-(3*H*)4-one (**5**). The bromine of **5** was displaced by various nucleophiles to give 6-substituted imidazo[4,5-*d*]-*v*-triazine nucleosides such as 6-azido-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[4,5-*d*]-*v*-triazine-(3*H*)4-one (**6**), 6-methoxy-7-β-D-ribofuranosylimidazo[4,5-*d*]-*v*-triazin-(3*H*)4-one (**9**), 7-β-D-ribofuranosylimidazo[4,5-*d*]-*v*-triazine-4,6-dione (**11**), and 6-thio-7-β-D-ribofuranosylimidazo[4,5-*d*]-*v*-triazin-(3*H*)4-one (**12**). Compound **6** in the presence of hydrogen and Pd/C was reduced to corresponding 6-amino-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[4,5-*d*]-*v*-triazin-(3*H*)4-one (**7**). Compounds **7** and **9** under the influence of hydrogen and Raney Ni were ring opened to give previously unreported 2,5-diamino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (**8**) and 5-amino-2-methoxy-1-β-D-ribofuranosylimidazole-4-carboxamide (**10**), respectively.

During the past few years, based on the original work of Buchanan and his colleagues,[1] there have been series of significant papers by Shaw and coworkers[2,3] on the synthesis of imidazole nucleosides related to the key intermediates in the *de novo* purine biosynthetic pathway. Relatively few studies have been made on the chemical modifications of these intermediates due to their difficult accessibility.[4] 5-Amino-1-β-D-ribofuranosylimidazole-4-carboxamide (AICA riboside) (**1**) is of special interest due to its central role[1] and recent commercial availability.[5]

Several of the procedures described in the literature, for the synthesis of AICA riboside[6,7] and its derivatives[8–10] include the ring opening of purine nucleosides. Ikehara and Muneyama[11] reported the formation of a 2-methylsulfonyl AICA riboside derivative by the cleavage of the pyrimidine ring of 8-methylsulfonylguanosine with sodium *tert*-butoxide but the precise structure of the product was never determined. Thus, 2-substituted derivatives of 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide are until now unknown. In the present work we describe a novel and convenient route for the synthesis of certain 2-substituted AICA riboside derivatives by (1) direct electrophilic substitution and (2) by the ring opening of substituted 2-azapurine nucleosides.

Direct attempts to brominate 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide (**1**) in various solvents were discouraging, and resulted mainly in unidentified oxidation products. However, when 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide[12] (**1a**) was treated with *N*-bromoacetamide in anhydrous tetrahydrafuran at −10°, crystalline 5-amino-2-bromo-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (**3**) was obtained in 70% yield. Subsequent deacetylation with a catalytic amount of sodium methoxide in methanol afforded the nucleoside, 5-amino-2-bromo-1-β-D-ribofuranosylimidazole-4-carboxamide (**3a**). In a similar experiment, using *N*-chlorosuccinimide as the halogenating agent, the corresponding 5-amino-2-chloro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (**4**) and 5-amino-2-chloro-1-β-D-ribofuranosylimidazole-4-carboxamide (**4a**) were prepared.

As expected, the direct displacement of bromine atom from **3** or **3a** by various nucleophiles was unsuccessful, *e.g.*, several hours reflux of **3** with excess 2 *M* methanolic sodium methoxide showed the presence of **3a** as the only reaction product. The ease by which the bromine would be displaced in such a molecule would depend upon lowering the electron density at the C-2 position. An earlier report from this laboratory[13] described the ring annulation of AICA riboside (**1**) *via* diazotization to give 7-(β-D-ribofuranosyl)imidazo-[4,5-*d*]-*v*-triazin-4-one (**2**, 2-azainosine). We subsequently discovered that 2-azainosine could readily be ring opened and reconverted into AICA riboside by hydrogenation in the presence of Raney Ni. In a similar experiment, when Raney Ni was replaced by Pd/C (10%) the starting material was recovered unchanged. Thus it was expected that 2-bromo-AICA riboside (**3a**) could be first converted to 6-bromo-7-(β-D-ribofuranosyl)imidazo[4,5-*d*]-*v*-triazin-4-one (**5a**) which renders the bromine susceptible to nucleophilic attack. Subsequent hydrogenolysis in the presence of Raney Ni should provide the required 2-substituted derivative of AICA riboside.